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## A clinical trial to measure effectivity of oral levodopa/carbidopa on visual sensory functioning in subjects with amblyopia and/or anomalous correspondence: Protocols and case report

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# A clinical trial to measure effectivity of oral levodopa/carbidopa on visual sensory functioning in subjects with amblyopia and/or anomalous correspondence: Protocols and case report

## Abstract

**BACKGROUND:** Recent research has suggested that levodopa/carbidopa (L-dopa), an oral medication that is prescribed for Parkinson's disease, may be effective alternative to treating amblyopia. The goal of this study is to provide clinical protocols to determine whether oral L-dopa can be used to augment standard occlusion therapy to improve sensory function for amblyopic patients with or without strabismus and anomalous correspondence (AC). The study design is a single-masked and pseudo-randomized with control subjects. It was designed to have a 13 week duration period. Visual sensory function will be evaluated in terms of visual acuities, contrast sensitivity, level of stereopsis, and suppression behavior. Amblyopic patients will then be screened through a battery of tests to assess the presence and depth of anomalous correspondence. Patients were excluded if screening tests indicate a poor prognosis for binocular integration after occlusion therapy, and if subjects have any contraindication to L-dopa use. Although this study was originally designed with the intension of enrolling 30 amblyopic subjects, it was modified to be a study design and case report.

**CASE REPORT:** A 67 year-old man came to Pacific University to improve the alignment of a longstanding Left exotropia and left hypotropia. Two months after strabismus surgery the patient began taking the combination drug L-dopa/ C-dopa to improve the sensory function of his visual system with the ultimate goal to sustain the improved ocular alignment achieved from the strabismus surgery. At the end of the 18 week L-dopa trial the patient's acuities were relatively unchanged from pre-study levels. Minimal changes were also noted in contrast sensitivity as well as objective and subjective ocular alignment measurements. The subject didn't note any subjective improvement in vision.

**CONCLUSIONS:** Patients that suffer from amblyopia, strabismus, and ananomalous correspondence often are challenging cases to manage for clinicians in terms of meeting patient goals or expectations. Our study focuses on an adjunctive therapy that may lead the way to provide a more beneficial outcome for these patients than standard occlusion therapy alone. It could allow for less aggressive approaches in vision therapy while reducing treatment time. It may also increase success rates in strabismus surgery and reduce the overall number of surgeries required to obtain ocular alignment. At the end of our clinical trial there was little change noted in the Pilot subject's visual acuity, contrast sensitivity and measured angle of strabismus.

## Degree Type

Thesis

## Degree Name

Master of Science in Vision Science

## Committee Chair

Hannu Laukkanen

## Keywords

amblyopia, anomalous correspondence, strabismus, visual sensory function, occlusion therapy

## Subject Categories

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A CLINICAL TRIAL TO MEASURE EFFECTIVITY OF ORAL  
LEVODOPA/CARBIDOPA ON VISUAL SENSORY FUNCTIONING IN SUBJECTS  
WITH AMBLYOPIA AND/ OR ANOMALOUS CORRESPONDENCE: PROTOCOLS  
AND CASE REPORT

BY

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DOLLY HSU-CHEN

A thesis submitted to the faculty of the  
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## **BIOGRAPHY**

Jeffrey Holland was born in Boulder Colorado November 29<sup>th</sup>, 1968. He attended Colorado State University from 1987 to 1990 and the University of Colorado from 1990 to 1992. He received a bachelors of arts degree from the University of Colorado in 1992 in Economics with the equivalent of a minor in Biology and French. He worked in a law firm in Paris France in 1993 as a bilingual legal assistant at a firm specializing in maritime law. After returning to the United States he worked in the financial planning department of a bank from 1994-1998 where he held a series 7 license as well as series 63 and a variable life insurance license. In 1998 he was admitted to the Pacific University College of Optometry in Forest Grove Oregon. He is a member of the American Optometric Association, AOA-PAC, COVD, and the Colorado Optometric Association. He was the president of Amigos Eye Care, a non-profit humanitarian organization affiliated with Pacific University, from March 2000 to March of 2001. He has been on humanitarian missions to Kazakstan, Honduras and Chile. His future plans are to return to Colorado to work with his father in private optometric practice in Boulder Colorado upon graduation from Pacific University in May of 2002.

## **BIOGRAPHY**

Dolly Hsiao-Ying Hsu-Chen was born in Taipei, Taiwan in 1970. After growing up for a brief period in Toronto, Canada, Dolly attended middle and high school in Bethesda, Maryland where her family now resides. Dolly graduated from Tufts University (Class of 1992) with a B.A. in Asian Studies. Dolly gained experience as an ophthalmic technician while she worked in the office of Dr. Michael Berenhaus, the president of the Maryland Optometric Association.

At Pacific University, Dolly was a member of Amigos and participated in a humanitarian mission to Costa Rica. For her first externship, Dolly was at Tyndall AFB in Florida for training in primary care optometry. For her second external rotation, Dolly traveled to OMNI Eye Services, an ocular disease referral center in Chattanooga, Tennessee. Upon graduation, Dolly plans to work for several years and then complete a residency.

## **ABSTRACT**

### ***BACKGROUND:***

Recent research has suggested that levodopa/carbidopa (L-dopa), an oral medication that is prescribed for Parkinson's disease, may be effective alternative to treating amblyopia. The goal of this study is to provide clinical protocols to determine whether oral L-dopa can be used to augment standard occlusion therapy to improve sensory function for amblyopic patients with or without strabismus and anomalous correspondence (AC). The study design is a single-masked and pseudo-randomized with control subjects. It was designed to have a 13 week duration period. Visual sensory function will be evaluated in terms of visual acuities, contrast sensitivity, level of stereopsis, and suppression behavior. Amblyopic patients will then be screened through a battery of tests to assess the presence and depth of anomalous correspondence. Patients were excluded if screening tests indicate a poor prognosis for binocular integration after occlusion therapy, and if subjects have any contraindication to L-dopa use. Although this study was originally designed with the intension of enrolling 30 amblyopic subjects, it was modified to be a study design and case report.

### ***CASE REPORT:***

A 67 year-old man came to Pacific University to improve the alignment of a longstanding Left exotropia and left hypotropia. Two months after strabismus surgery the patient began taking the combination drug L-dopa/ C-dopa to improve the sensory function of his visual system with the ultimate goal to sustain the improved ocular alignment achieved from the strabismus surgery. At the end of the 18 week L-dopa trial the patient's acuities were relatively unchanged from pre-study levels. Minimal changes



were also noted in contrast sensitivity as well as objective and subjective ocular alignment measurements. The subject didn't note any subjective improvement in vision.

### ***CONCLUSIONS:***

Patients that suffer from amblyopia, strabismus, and anomalous correspondence often are challenging cases to manage for clinicians in terms of meeting patient goals or expectations. Our study focuses on an adjunctive therapy that may lead the way to provide a more beneficial outcome for these patients than standard occlusion therapy alone. It could allow for less aggressive approaches in vision therapy while reducing treatment time. It may also increase success rates in strabismus surgery and reduce the overall number of surgeries required to obtain ocular alignment. At the end of our clinical trial there was little change noted in the Pilot subject's visual acuity, contrast sensitivity and measured angle of strabismus.

**Key Words:** Amblyopia, Anomalous correspondence, strabismus, visual sensory function, occlusion therapy

### **Acknowledgements:**

We would like to acknowledge the following individuals for their contributions to this study:

Hannu Laukkanen, O.D., M.Ed., F.A.A.O.

Richard London, M.A., O.D., F.A.A.O.

Thomas Lenart, M.D., PhD.

We would also like to acknowledge Beta Sigma Kappa for their financial contribution to this study.

## **Introduction:**

Amblyopia is a non-organic reduction in visual acuity (as well as other visual sensory functions) not correctable by refractive means and usually is the result of light or form deprivation, strabismus or uncorrected anisometropia in early childhood. Anomalous correspondence (AC) is a sensory adaptation that is generally thought to be a response to ocular misalignment. It is thought to be a sensory defense mechanism against diplopia that preserves rudimentary binocular visual functions. Adult amblyopes and patients who have AC have a poorer prognosis with either surgery or vision therapy. Strabismic patients with dense amblyopia or AC typically require multiple surgeries to correct the strabismus. This arises often to poor sensory fusion status or suppression allowing the eyes to drift out of alignment after surgery. Thus, any improvement in the sensory system, i.e. acuity, contrast sensitivity, fusional ability or reduction in anomalous behavior will be of great benefit in the treatment of AC patients; it will allow less aggressive approaches, shorter treatment time, and potentially fewer surgeries to obtain alignment.

Recent research has suggested that levodopa/carbidopa (L-dopa), an oral medication that is prescribed for Parkinson's disease, may be effective in treating amblyopia in adults when administered in conjunction with occlusion therapy<sup>1-10, 15-18</sup>. L-dopa is a precursor for the catecholamine dopamine, a neurotransmitter known to influence the visual system at the retina and at cortical levels. Carbidopa is a peripheral decarboxylase inhibitor that prevents the breakdown of levodopa at peripheral sites and allows more levodopa to cross the blood brain barrier. In studies L-dopa has improved visual acuity on average in the

amblyopic eye by two lines, and one-half line in the dominant eye as well as a decrease in suppression tendencies<sup>1</sup>. All results to date indicate the visual function improvement is permanent to at least 6 months, although long-term results are not known. This recent and not widely known treatment could prove important for hard-to-correct older amblyopic as well as anomalous correspondence patients.

The purpose of these testing protocols is to study the affects of L-dopa administration on the visual sensory functions of subjects with amblyopia and (or) anomalous correspondence. We hypothesize that patients who are undergoing occlusion therapy and have reached a plateau or are having difficulty with patching may be able to obtain additional sensory function improvement from addition of L-dopa therapy. We will measure visual outcomes in terms of visual acuity, contrast sensitivity, suppression behavior, stereopsis, and level of anomalous correspondence (if present). If these clinical trial results indicated that the combination of L-dopa and occlusion will provide a more beneficial outcome than standard occlusion therapy alone, it would be of great benefit to this patient group.

## **Methods**

These are the original methods for the multi-center design that was intended to have 30 subjects. The tests used for the experiment are standard optometric procedures with rare associated risks. These tests are commonly referenced in optometric texts, journal articles, and classroom lectures on binocular vision. The tests selected are divided into four categories: determination of fusion potential, evaluation of sensory function, qualifying tests for anomalous correspondence, and measuring tests for anomalous correspondence.

To assess if bifoveal fusion potential is present, we used the Clement-Clarke Synoptophore and the random dot butterfly stereo acuity test.

To measure sensory function we used the BVAT (Binocular Video Acuity Tester). This measured visual acuities, contrast sensitivities, level of distance stereopsis, suppression behavior, and measurement of crowding with and without control bars.

The qualifying tests for anomalous correspondence include: BVAT acuity and sensitivity testing 2) Macular Integrity Tester (Haidinger's Brushes), 3) Visuoscopy, 4) Visagraph, and 5) Dissociated Red Lens Test.

Tests for measurement of anomalous correspondence include: 1) Synoptophore (Major Amblyoscope), 2) Hering-Bielchowsky (HBAIT) as well as Brock-Givner After-Image

Tests, 3) Red-Green Glasses Anomalous Correspondence Test, 4) Worth 4-Dot Test and 5) Bagolini Striated Lens test.

The testing protocols are as follows:

**Testing for Determination of Fusion & Sensory Potential:**

**Clement-Clarke Synoptophore to assess if bifoveal fusion potential is present<sup>12</sup>**

1. Present subject with first and second degree targets at the objective angle of deviation.
2. Patient reports simultaneous perception if viewing a first degree target or if targets fuse easily into a single target with a second degree target.
3. If the patient reports the two images appear to jump when overlapping of targets occurs this may indicate the presence of horror fusionis.

**Random-Dot Stereo Optical Butterfly Test <sup>12</sup>**

1. Subject will wear polarized lenses.
2. Stereo test will be conducted at 40cm.
3. Subject views random dot butterfly test and highest level of subjective stereo acuity.

4. Stereo acuity will be recorded in arc seconds, or if suppression is present this was noted.

#### **Determination of Sensory Function:**

##### **BVAT Acuity and Contrast Sensitivity Testing<sup>19</sup>**

1. Monocular and binocular acuities were taken at standard 6 meter testing distance under standard room illumination.
2. Distance Stereopsis was tested by wirt stereo circles.
3. Check for suppression was noted with liquid crystal goggles.
4. Contrast Sensitivity  
Initial contrast sensitivity testing stimulus level is two lines above the previously determined BVAT best monocular acuity level.
5. Crowding effect was tested with and without control bars for the best visual acuity.

## Qualifying tests for Anomalous Correspondence:

### BVAT acuity and sensitivity testing<sup>19</sup>

1. Data was used as measured above.

### Bernell Macular Integrity Tester and Trainer (MITT)<sup>11</sup>

1. Testing was performed under dim conditions at 50 cm monocularly.
2. The non-amblyopic eye was tested first to demonstrate the appearance of the brushes.
3. Subject was directed to look at a fixation point and perceive the rotating brushes. If they cannot appreciate the rotating brushes then a blue filter or blue lenses was placed before the subject. If the subject still wasn't able to appreciate the rotating brushes then fixation status in the amblyopic eye is not possible.
4. The amblyopic eye is tested again by asking the subject to regard the fixation point and note where the brushes are seen. If the pointer and brushes are superimposed over the fixation target then the subject has central fixation. If the brushes and pointer are not over the fixation target it indicates eccentric fixation. To calculate the amount of eccentric fixation use the following formula:  $\text{Eccentric fixation (prism diopters)} = 100 \times (\text{separation in centimeters}) / (\text{test distance in meters})$ .



### **Visuoscopy (Keeler Ophthalmoscope)**<sup>13</sup>

1. Occlude the preferred eye.
2. Have patient look directly at center of projected pattern of reticule and hold fixation as steady as possible.
3. Clinician objectively determines the positioning of the fovea with respect to the center of the reticule.
4. In general the target reticule separation is 1 prism diopter magnitude.
5. If the subject has eccentric fixation then the direction and magnitude is notated.
6. The steadiness of fixation should be notated. If unsteady, the amplitude and type of oscillations should be documented.

### **Taylor Associates Visagraph2 Testing Protocol**<sup>20</sup>

The visagraph2 will be used to note stability of fixation.

1. Subject is directed to fixate at a center X for 10 seconds without any eye movement. The ability of the subject to do so will exhibit the level of control a subject has over his/her visual mechanism.
2. The test will first be run monocularly with the good eye.
3. Next run the test monocularly with the deviant eye.
4. Finally the test will be run binocularly (if possible).

### **Dissociated Red Lens Test**<sup>11-12</sup>

1. An objective distance cover test was performed and neutralized with prism bars at standard illumination over the patient's best-corrected lens.
2. A red lens and 10-diopter base up prism are placed before the fixating eye while the patient views a light at 6 meters.
3. Patient was asked to describe the position of the two lights. If no horizontal separation is present then the subjective angle is zero, and harmonious anomalous correspondence exists (if there is a strabismus present- verified by the douse test).
4. If the patient has uncrossed diplopia base-out prisms were added until the red and white lights are vertically aligned. Base-in prisms were added for crossed diplopia.

5. If the amount and direction of prism necessary to align the lights vertically is commensurate with the objective angle, as measured with the alternating cover test with prisms at the same fixation distance with the same eye fixating, then normal correspondence exists. If they differ by more than 4 prism diopters then unharmonious correspondence exists.

#### **Tests for Measurement of Anomalous Correspondence:**

##### **Synoptophore Test (Clement-Clarke)**<sup>11-12</sup>

1. Determine the status of retinal correspondence by measuring the objective angle. Superimposition of two first-degree targets is used.
2. The target with the Clement-Clarke guard house (for instance) should be in front of the non-preferred eye and the target of the guard should be in front of the preferred eye.
3. The preferred eye is locked in the ortho position.
4. The examiner alternately turns the illumination of each target on and off while moving the tube of the deviated eye until the two images are superimposed.

The absence of any fixation movement indicates that the objective angle has been obtained, as read off the scale on the instrument.

5. The subjective angle is determined by having the patient move the tube before the deviating eye until the targets appear superimposed.
6. If objective and subjective angles are equal this indicates normal correspondence. If objective and subjective angles are unequal by 4 prism diopters or more this indicates anomalous correspondence.
7. A subjective setting of zero by a strabismic patient indicates harmonious AC, whereas a subjective setting between zero and the objective angles indicates unharmonious AC.
8. Once the subjective angle has been determined and the targets are superimposed the retinal correspondence can be confirmed by briefly extinguishing the target before the preferred eye and watching for any movement of the other eye (Douse test). No movement indicates normal correspondence, and movement indicates AC.
9. The objective angle that was previously determined is placed in the synoptophore such that both images are placed on the foveae. In the presence of normal correspondence, superimposition of the targets will occur. In AC diplopia is reported. Esotropic patients will perceive crossed images. Exotropic patients will perceive uncrossed images.

**Hering Bielchowsky (HBAIT) & Brock-Givner After-Image Test (Wayne Engineering Flash Test Unit)<sup>11</sup>**

The Brock-Givner afterimage directly measures the angle of anomaly by using afterimages (AIs) to tag the visual direction of the foveae.

1. Occlude the deviating eye and have the patient look at a central fixation point on a modified photoflash oriented horizontally. The central flash must be opaque to produce a small gap in the AI. Flash the unit. The resultant horizontal afterimage will tag the fovea, assuming that the patient was accurately fixating.
2. Switch the occluder, and repeat the procedure, placing a vertical after image on the deviated eye. (Remember that EF will affect this portion of the test, and the measured angle of anomaly must be corrected.)
3. Uncover both eyes and ask the patient whether both AIs are seen at the same time. If not, the examiner can have the patient blink quickly or strobe the room lights (by alternately lowering and raising the room illumination every 3 seconds) to help the patient appreciate the AIs.
4. Instruct the patient to fixate a small fixation point on a centimeter scale on a blank wall at a distance of 1m. The patient should report the horizontal AI centered over the fixation point. The negative AI is more reliable in routine testing than is the positive AI. The negative AI is seen in a lighted room and

the positive AI is seen in a darkened room. The patient is asked to pay attention to the negative AI as the room illumination is increased.

5. Have the patient report where the vertical AI is positioned. The number on the scale will represent the angle of anomaly in prism diopters (Brock-Givner Test).

### **Red-Green Glasses Anomalous Correspondence Test**<sup>11-12</sup>

1. Patient views an illuminated gray featureless screen at distance of 2 meters with red-green glasses.
2. A patient with AC will report a split field, one side red and one side green
3. A patient with normal retinal correspondence will report an appreciation of color fusion or luster.
4. Patient may see only red or only green, indicating suppression.

### **Worth 4-Dot Test**<sup>11-12</sup>

1. Testing is performed at 50 centimeters and/ or 6 meters.
2. Patient wears red/ green glasses
3. The presence of 4 dots in the presence of constant strabismus indicates a subjective angle of zero and harmonious anomalous correspondence.

4. The position of the eyes must be noted at the time fusion is reported.
5. If the patient reports 5 dots simultaneously a subjective angle exists and prisms can be used to differentiate normal correspondence from anomalous correspondence.
6. Normal correspondence is diagnosed if the lights are superimposed into 4, with prisms equal to the objective angle, and no movement is noted on unilateral cover (douse) test of the preferred eye.
7. The diagnosis of unharmonious anomalous correspondence is made if a significantly different prism (more than 4 PD) allows superimposition and with that prism the unilateral cover test shows movement.

#### **Bagolini Striated Lenses (Bernell)<sup>12-13</sup>**

1. A Bagolini lens is placed in front of each eye with the striations 90 degrees apart.
2. The patient views a penlight at 1 meter.
2. The patient's vision of the test target is relatively unimpaired, and the light source appears as two streaks at right angles to each other.

3. The number of streaks and lights perceived (1 or 2) is noted. If only one streak is seen or if a missing section of a streak is noted then suppression is present.
4. If the two streaks cross at the intersection of one light this indicates normal correspondence if no strabismic deviation is present. It indicates harmonious anomalous correspondence if a strabismic deviation is present.
5. If one light is seen at the intersection of the two streaks then unilaterally cover the fixating eye (douse test). A corresponding movement of the deviant eye confirms the presence of AC.
6. If two lights are seen above the intersection this indicates esotropia with normal correspondence.
7. If the two lights are seen below the intersection of the two lines this indicates exotropia with normal correspondence.

#### **Selection of Subjects and Methods of Randomization:**

Subjects were recruited at three sites: Pacific University College of Optometry Family Vision Center, Pediatric and Strabismus Referral Center in conjunction with Pacific University Portland Family Vision Center, and the office of Dr. Thomas Lenart at The Children's Eye Doctor. Subjects eligible for selection were intended to be amblyopic



who were age 4 or older. Subjects were allowed to enroll in the study if they did not meet any conditions in the exclusion criteria referenced below.

Eligible subjects were intended to be randomly placed into three groups by a third party:

1) control group who receive no therapy, 2) a group who uses occlusion therapy only and 3) a group who uses oral L-dopa only. It was intended that a minimum of 30 subjects per group be enrolled to achieve statistical significance.

### **Experimental Design**

The experiment design contained three phases. In the Phase I, the three groups of subjects were to be screened through the previously referenced battery of tests to obtain baseline sensory function ability and to indicate the presence and depth of anomalous correspondence.

Baseline group index numbers were to be calculated for each of the sensory tests performed (see calculations methods in the results section). An anomalous correspondence index number was also to be calculated for each subject identified with AC, based on the number of positive results for each of the AC screening tests. These indices were to be compared to one another for the purposes of assessing effectiveness of the various therapies.

In Phase II data was to be gathered from the three test groups. All tests that were performed at baseline were to be retested at week 3.5 and week 7.

Phase III was to involve a follow up visit 6 weeks after termination of therapy. During the follow up visit all tests that were performed at baseline were retested to assess the stability of any improvements in sensory functioning and or reduction in the angle of anomaly achieved at the end of phase II.

Subjects in the occlusion therapy group were to have the non-amblyopic eye occluded for 3 hours per day in the evenings for the 7-week period. They were to be given a brief questionnaire at each of the visits to determine the level of compliance (*see forms appendix A*).

Subjects in the L-dopa therapy group were given L-dopa at the dosage of 0.75 mg/kg body weight with 25% carbidopa three times per day after a meal or snack. (In Leguire's studies subjects received L-dopa based on body weight and averaged 0.75 mg/kg body weight three times per day for 12 weeks).<sup>1</sup> This dosage is the same or about 25% less than that used in other previous L-dopa studies, and is known to be an effective and well-tolerated dosage. Compliance with the drug regimen was strictly monitored by the prescribing physician when refilling the prescriptions. Our protocol required that subjects in the L-dopa group have a physical examination prior to beginning L-dopa therapy; weight, blood pressure, body temperature, heart rate and respiration rate be recorded to monitor for any health changes during the testing period. The patients were

responsible for the cost of the medications and the primary care physician's professional fees.

The L-dopa dosage was based on body weight and was considered to be in the effective therapeutic range according to previous studies.<sup>1-9</sup> Subjects were instructed to take the individual dose with a meal or snack to minimize nausea and emesis. The liquid formulation was used in the present study to ease dosing requirements. Subjects were given two cans of Sustacal or Ensure, a high protein drink, and instructed to drink one can in the event of possible adverse side effects. Based on case reports, high protein substances (e.g., Sustacal) compete for transport with L-dopa in the gut and at the blood-brain barrier, thereby reducing the pharmacodynamics of L-dopa and presumably the adverse side effects<sup>5</sup>. Subjects were monitored for adverse effects to drug therapy at each subsequent testing visit or on an emergency basis. They were educated for signs and symptoms that may indicate an adverse drug reaction. In the event of an adverse drug reaction, subjects were advised to contact their primary care physician.

### **Risks and Exclusion Criteria:**

Description of potential risks to subjects primarily entails discussing medical risks and visual risks. Other risks to the patient we will acknowledge include loss of confidentiality, and environmental risks from being present in an optometry office. In

recognition of the potential risks, we also employed measures to monitor the subjects and reduce risks.

Medical risks involve the side effects of L-dopa. This drug is FDA approved and is currently used as a treatment of choice in Parkinson's patients. We will inform the subject that L-dopa is not typically used for subjects with amblyopia or anomalous correspondence. The use of L-dopa for these patients is still considered experimental. Risks related to the L-dopa in decreasing prevalence include from data compiled by Leguire et al from 5 studies<sup>1-5</sup>: headache, tiredness, mood changes, nausea, dizziness, dry mouth, emesis (once per 1500 ingested capsules), restlessness, and nightmares. Other rare side effects are also noted. These rare side effects of L-dopa ingestion typically occur with much larger doses. As reported in the adult Parkinson's disease literature<sup>14</sup>, they include: chewing, gnawing, involuntary movements, twisting, tongue or mouth movements, movements of feet hands or shoulders, muscle twitching, muscle jerks during sleep, hand tremors, various psychiatric disturbances, anxiety, memory loss, agitation, confusion, inability to sleep, mental depression, euphoria, gastrointestinal effects, loss of appetite, weight loss, and possible decreased white blood cell count. Leguire et al<sup>1</sup> have not observed any changes in the standard laboratory tests of the 41 pediatric subjects tested to date. The above clinical adverse experiences occurring in 1 percent or greater of the adult Parkinson's population is reference in *Table 1*, which will be provided to the patient in the Risk Disclosure document. We informed the subject that all the listed potential side effects are reversible with discontinuation of the use of L-dopa.

The visual risks include intractable diplopia, horror fusionis, and unilateral diplopia. Intractable diplopia is a rare type of diplopia where the subject no longer exhibits suppression in the amblyopic eye and cannot achieve sensory fusion. Subjects were pre-screened for some ability to achieve fusion before being accepted as a test subject. Minimizing intractable diplopia was achieved through exclusion of deeply embedded AC subjects as measured by the AC index, on a case-by-case basis. Horror fusionis is a rare and specific type of inability to fuse that is characterized by an avoidance of bifoveal stimulation and an absence of suppression. Subjects were pre-screened for ability to achieve first-degree fusion before being accepted as a test subject. Subjects unable to achieve sensory fusion via the synoptophore may not be good candidates to participate in the study. These individuals may experience horror fusionis with L-dopa and binocular training therapy and will be excluded from the study. Unilateral diplopia is a side effect that may occur during therapy as the subject is trained to discontinue use of the anomalous correspondent point of the amblyopic eye. This is an expected and typically temporary phenomenon in AC subjects during foveal anti-suppression training. Diplopia problems were monitored by an optometric intern or faculty member at the Pacific University Family Vision Clinic.

In order to protect confidentiality individual names of participants were not be disclosed to anyone outside of the investigators. In the event of publication of this study, the subject's identification will not be revealed.

If there are important new findings during the course of this study that might affect the subject's willingness to continue to participate, the investigators will immediately notify the subjects. Participation in this study is voluntary. The subject was able to refuse to take part in any part of the study or stop participation at any time. The subject was asked to notify the investigators immediately if he or she chose to discontinue participation in the study.

### **Limitations of the Methods Employed:**

Some of the limitations that could have been encountered from the methods employed in this study are as follows:

- Patient non-compliance with use or dosage of medications:

This is potentially a large source of variability in our study. In order to increase patient compliance for medication we have asked patients to fill out a survey form that questions their compliance with the dosing of the medication. (See appendix A for forms)

- Patient non-compliance with occlusion therapy:

This may also be a significant source of variability in the study. Patients were to be asked at each visit to complete a form that will assess their compliance with patching.

- Clinician error in assessing objective tests:

The nature of anomalous correspondence requires a fairly skilled clinician to correctly assess the presence and magnitude of AC. Skills in AC assessment can be variable from one clinician to another.

- Patient fatigue during testing:

The entire battery of testing can be quite lengthy and patient fatigue is a factor that may limit the reliability of the data acquired.

- Poor comprehension of testing instructions by patient:

Amblyopia and AC testing is fairly complex and requires a subjects attention and understanding of the instructions to evoke good responses. Poor communication by the testing clinician can limit the validity of the data.

- Inconsistent testing conditions:

While we have attempted to give step-by-step instructions in order to maintain consistent testing methods, each clinic does have different resources and environments. This may come in the form of different equipment, different illumination, projector and chart differences, etc....

- Equipment error and calibration discrepancies:

Different instrumentation may have given varying results. Instruments that are out of calibration may have yielded inaccurate results.



## **Results:**

### **Calculation Methods for Group Comparison:**

The results from the battery of tests performed on each of the subjects in the three experimental groups as follows:

Visual acuity was taken by means of the BVAT (logmar) on all subjects for line as well as single letter acuity both with and without crowding bars. The best acuity level was to be averaged for each of the three groups (control group, occlusion therapy only group, and occlusion with L-dopa group). This was to be done at baseline visit (week 0), at 3.5 weeks, 7 weeks and 13 weeks.

Contrast Sensitivity was measured by the BVAT on all subjects using a test stimulus of two lines above threshold visual acuity. It was recorded monocularly as a percentage of BVAT full test stimulus contrast. This was to be averaged for each of the three groups and will be performed at the baseline visit (week 0), at 3.5 weeks, 7 weeks, and 13 weeks.

Distance stereopsis was performed by the BVAT on all subjects and recorded in the lowest arc seconds visible to the subject. This was to be averaged for all subjects in each of the 3 groups. This was to be performed at week 0, 3.5, 7, and 13

Suppression was checked by means of the suppression checks built into the BVAT using the liquid crystal goggles and testing suppression of letters at various acuity demands. A value of +1.0 is given to subjects exhibiting suppression. A value of 0 is given to subjects who do not show suppression. For each group the sum of the values was to be calculated and divided by the subjects in the group. This will give a value of 1.0 if all subjects in a group suppress and a value of 0 if no subjects show suppression. This is multiplied by 100% to give percentage of subjects exhibiting suppression.

#### **Calculation of the anomalous correspondence index:**

It was intended that the anomalous correspondence index was to be calculated for each subject in each of the three groups. The AC index consist of results for each of the following tests: Synoptophore, Hering-Bielchowsky After-Image Test, The Worth 4-Dot Test and Bagolini Striated Lens Test. A positive AC response receives a value of the difference between the objective and subjective angles. An eso AC deviation receives a positive number and an exo AC deviation receives a negative number. The index score is the sum of the values corresponding to each test divided by the number of AC tests performed. This gives a score that measures both presence and magnitude of the angle of anomaly. All tests have equal weighting as far as the calculations of the AC index.

The sum of each AC index for all subjects in a group was to be divided by the number of subjects in the corresponding group. This will give an average AC index value for each

of the three test groups, which was to be used for comparisons between groups and within groups.

Comparisons were to be made from the above referenced data as follows:

Mean group index data for both sensory function and AC was to be compared between the three groups at each time interval. A comparison was to be made at baseline (0 weeks) 3.5 weeks, 7 weeks, and at 13 weeks. This data was to be compared by an analysis of variance (ANOVA) test using a two-tailed hypothesis with a p-value of ( $<0.05$ ).

Mean intra-group comparisons was also to be made between baseline and 3.5 weeks, baseline and 7 weeks, and baseline and 13 weeks. A final comparison was to be made between 7 weeks and 13 weeks to assess stability after cessation of therapy. The data was to be analyzed with a t-test comparison using a two-tailed hypothesis and a p-value of ( $<0.05$ ).

## *Case Report*

### Patient History

A 67 year-old Caucasian male, FN, came to the Pacific University clinic with a chief concern of ocular misalignment for cosmetic reasons. He reported constant diplopia with symptoms of the left image interfering with the right image. The misalignment problem began over 20 years ago but the symptoms of the diplopia had become more noticeable over the previous year. FN had undergone strabismus surgery at age 19 for a left esotropia, afterwards the patient reported good cosmetic alignment. Subsequently he underwent a second strabismus surgery at age 67 for a 55<sup>Δ</sup> consecutive left exotropia and 4<sup>Δ</sup> left hypotropia. He also reported using direct patching therapy of the right eye for three years in elementary school. FN wore bifocals full time for driving and for near work.

Personal medical history includes hypertension of which is treated with an oral beta blocker. Otherwise he was in good health.

Following vision therapy to improve peripheral fusion, FN inquired about the chance of improving visual acuity in the amblyopic eye. He felt that he would be better able to fuse if the visual acuity was more equal.

The patient was given several options and elected to try the L-dopa/ C-dopa therapy with a goal of improving both central and peripheral acuity. If successful this would improve

the long-term post-operative outcome of the most recent strabismus surgery, as good sensory fusion ability is essential in sustaining oculomotor alignment.

### **Exam at Week 0 of L-dopa Trial**

Prior to entering the L-dopa/ carbadopa study, FN presented at the initial visit with habitual correction of OD PI  $-1.00 \times 140$  add  $+2.25$ , OS  $+2.00 -0.75 \times 056$  add  $+2.25$  giving BVAT distance line acuities of  $20/20^{-1}$  OD,  $20/30$  OS. He demonstrated no distance stereopsis with BVAT wirt circles, nor did he at near with the stereofly. Contrast sensitivity with BVAT using 2 lines above best acuity was 25% for both OD, OS.

All cover testing was performed without correction. Cover testing revealed that his post-operative objective residual angle was measured at  $3^{\Delta}$  left esotropia,  $10^{\Delta}$  left hypotropia in primary gaze at distance with a dissociated vertical deviation (DVD).

The crowding effect on acuity was tested also by BVAT giving  $20/20$  acuity OD for chart, line and letter. OS acuity was  $20/30$  chart,  $20/25 -3$  line, and  $20/25$  letter acuity.

Visuoscopy was attempted but an assessment was unobtainable due to poor foveal light reflex and small pupil size.

The dissociated red lens test objective angle was  $10^{\Delta}$  left hypotropia with no lateral movement, measured without correction. An estimation of the subjective angle was

placed at  $4^{\Delta}$  left esotropia with  $8^{\Delta}$  left hypotropia. With the objective prism in place the patient was unable to obtain fusion of the targets.  $2^{\Delta}$  BO was placed in front of the patient and he reported the red and white lights had changed positions laterally but again no fusion was ever noted.

Synoptophore testing yielded an objective angle of  $2^{\Delta}$  left esotropia with  $6^{\Delta}$  left hypotropia. Subjective angle measured at  $10^{\Delta}$  left esotropia with  $6^{\Delta}$  left hypotropia. The patient was able to achieve superimposition of first-degree targets briefly. This suggested he did not express horizontal fusion.

During the Worth 4-dot test the patient gave a response of 4 dots in the distance, with a constant vertical strabismus present. This may have suggested one of the dots was fused briefly. See figure 1-1. However at a test distance of 50 centimeters the patient reported 5 dots.

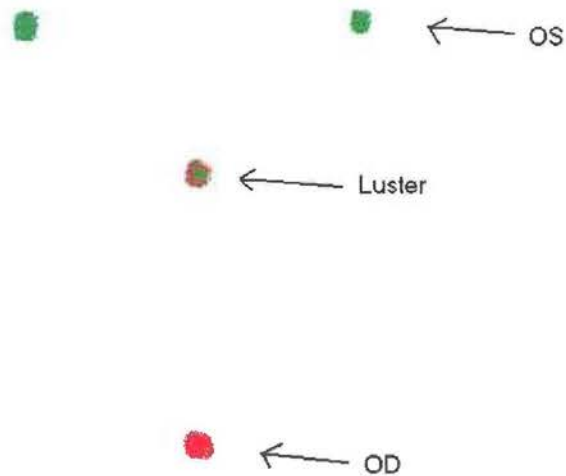
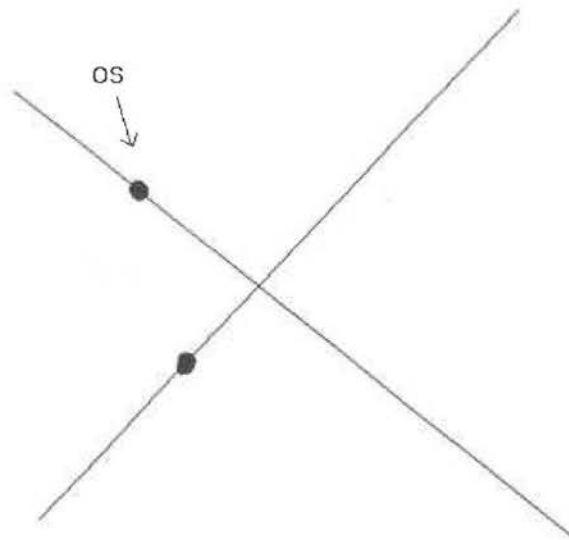


Figure 1-1 Worth Dot

Bagolini Striated Lens test revealed constant diplopia as two lights were seen. A sketch by the patient is demonstrated in figure 1-2 representing the patient's subjective perception. This suggested that FN was not suppressing either eye during binocular viewing. It also shows the presence of the left hypotropia.

The combination drug L-dopa/ C-dopa was initiated with 1 dose per day for 3 days, then 2 doses per day for 3 days, then 3 doses a day thereafter.



Patient's drawing of Bagolini percept.

Figure 1-2

### **Exam at Week 7 of L-dopa Trial**

At the start of the exam the patient was asked to complete a symptom check list. The patient reported one episode of dizziness, and an occasional flushed feeling.

BVAT acuities were OD 20/20 chart, line and letter. OS was 20/30<sup>-2</sup> line, and 20/20<sup>-2</sup> single letter.

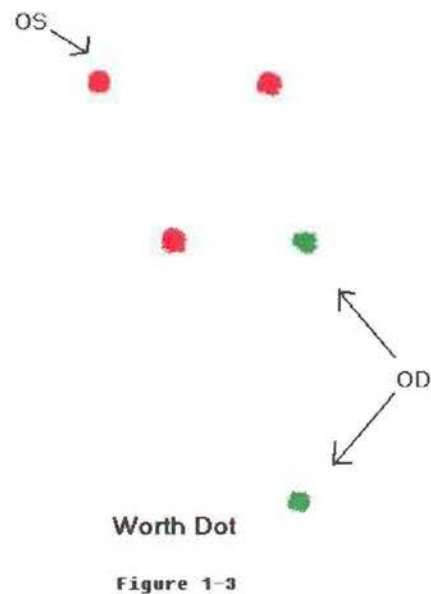
Contrast sensitivity was again tested on the BVAT at two lines above best acuity. OD tested at 20%, OS at 25%.

No distance or near stereopsis was obtainable with the BVAT or near stereofly.



Dissociated red lens test showed unsteady fixation with the objective angle measuring  $8^{\Delta}$  left hypotropia and no lateral movement. Subjective measure was  $8^{\Delta}$  to  $11^{\Delta}$  left hypotropia. The subject was unable to fuse the target and reported variations in the target position from slightly eso to slightly exo with only brief moments of fusion.

Worth 4-Dot gave a subjective response of 5 dots seen at distance. See figure 1-3.



Bagolini striated lens test was given and the patient drew a similar picture of the striated image as in the initial exam, see figure 1-2.

The patient continued taking the L-dopa/ C-dopa at 3 doses per day until the next scheduled exam.

### Exam at Week 18 of L-dopa Trial

The patient was again asked to complete a symptoms check list. The only side effect he reported was increased incidents of night dreams.

BVAT acuities were OD 20/20 chart, line and letter. OS 20/30 line, 20/25 single letter acuity. BVAT contrast sensitivity was OD 25% and OS 32%, again using two lines above best recorded acuity.

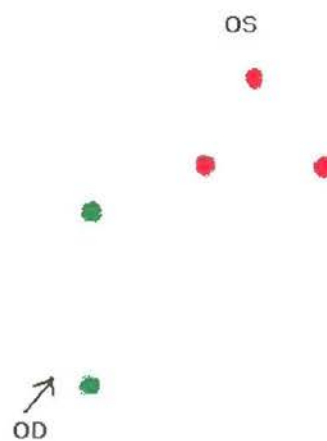
No distance or near stereopsis was achieved by the patient.

Distance cover testing gave objective angle of  $8^{\Delta}$  left hypotropia with no lateral movement. Near cover test was  $8^{\Delta}$  left hypotropia and  $2^{\Delta}$  left esotropia.

Dissociated red lens test gave a slight uncrossed diplopia response with no fusion ability with objective prism in place. Patient reported the subjective angle to be unstable and approximately the same as the objective finding.

Synoptophore objective angle was measured at  $8^{\Delta}$  left hypotropia with  $2^{\Delta}$  left esotropia. Subjective angle was found to be  $11^{\Delta}$  left hypotropia and  $7^{\Delta}$  left esotropia. The change from the week 0 subjective findings suggested a hypo direction shift in the patient's sensory perception may have occurred.

Worth 4-dot test showed 5 dots seen at both distance and near testing. The dots were dissociated and subjectively was reported as crossed indicating a subjective left exo and left hypo posture. See the figure 1-4 for the patient's perception of the test.



**Figure 1-4**

BVAT Contrast Sensitivity; two lines above threshold acuity

Eye Tested	Week 0	Week 7	Week 18
OD	25%	20%	25%
OS	25%	25%	32%

Measured Angle of Deviation via Synoptophore

Type of Measure	Week 0	Week 7	Week 18
<i>Objective angle</i>	2 <sup>Δ</sup> LET, 6 <sup>Δ</sup> LHoT	not tested	2 <sup>Δ</sup> LET, 8 <sup>Δ</sup> LHoT
<i>Subjective angle</i>	10 <sup>Δ</sup> LET, 6 <sup>Δ</sup> LHoT	not tested	7 <sup>Δ</sup> LET, 11 <sup>Δ</sup> LHoT

The overall result in the patient's best-corrected single letter acuity remained unchanged from before the L-dopa trial and at the end of the 18 week period. The patient did have a 2-3 letter improvement noted at week 7 that was not repeatable by week 18.

Contrast sensitivity also showed minimal change throughout the study with a slight improvement noted on the right eye at week 7. This improvement however was not repeatable at week 18. The left eye showed a slight decrease in overall contrast sensitivity from week 0 to week 18. Subjectively the patient did not notice any improvement in his vision.

Throughout the study the subject never demonstrated a measurable level of stereopsis via BVAT wirt circles at distance, nor titmus stereofly at near.

The subject demonstrated characteristics of anomalous correspondence based on the difference in measured objective and subjective angles with the synoptophore as well as dissociated red lens tests. This remains inconclusive though, as an accurate measure of eccentric fixation was not obtained. In any case, the patient was only able to achieve a fleeting sensory fusion status at best throughout the 18 week period. The red lens, synoptophore and worth dot tests all showed an unstable motor and sensory system as well.

The subject reported good compliance with dosing of the medication and throughout the study only reported mild side effects consisting mostly of increased dreaming at night. The original protocol of 13 weeks of taking the L-dopa was not followed as per the design of the study had intended because of scheduling difficulties encountered both with the patient and the principal examiners.

#### **Implications of the Results of the Study:**

This study was comprehensive in design with a goal of recruiting enough subjects to make statistical comparisons. Our original goal was to determine whether or not L-dopa could be used as an adjunctive therapy to standard occlusion treatment for amblyopic

patients with or without AC. Unfortunately we were only able to recruit only one experimental subject out of the three sites. It is hoped that future trial multi-center clinical trials will investigate the effects of L-dopa on sensory function. This novel oral medication-occlusion therapy approach may lead to changing the standard of care for patients suffering from amblyopia or anomalous correspondence.

### **Limitations of the Results:**

Given the insufficient enrollment in this study, theoretical limitations of the results of this study could of arose from:

- Assumptions that the test population is representative of the general population
- Assumptions that responses from the test population can be generalized to the larger population
- Assumption that increased foveal and peripheral sensitivity would decrease sessions required for vision therapy and surgeries required in strabismics.
- Assumption that an improved sensory function would ameliorate the quality of life experienced by amblyopic patients.

## **Discussion:**

The study is comprehensive in design, and in theory was seeking to recruit enough subjects with amblyopia and anomalous correspondence, to allow significant statistical analysis of findings. Ultimately, the goal of this study was to determine whether L-dopa could be used to augment standard occlusion therapy for amblyopic and/or anomalous correspondence patients. Test results may in the future be part of a large multi-center clinical trial examining L-Dopa augmentation of occlusion therapy for amblyopia.

Given only one experimental subject, we do not have sufficient data to either accept or reject the hypothesis of whether L-dopa is a useful adjunctive treatment in amblyopic or AC patients. We have presented the data we gathered from the one subject that enrolled in the L-dopa trial. The data from this subject are difficult to interpret as there were transient changes that occurred in the patient's sensory functioning during the trial.

This paper focuses on the background research, design and planning required to conduct a clinical trial to measure effectivity of oral L-dopa on visual sensory functioning. We have learned from the various obstacles that were encountered during this investigation. The following is a summery of important points that we noted and our impressions as a guide for future researchers.

*WE DID NOT GET ENOUGH PATIENTS FOR A STATISTICALLY SIGNIFICANT STUDY OWING TO THE RELATIVELY FEW NUMBERS OF PATIENTS WITH AMBLYOPIA AND ANOMALOUS CORRESPONDENCE IN THE GENERAL POPULATION WILLING TO PARTICIPATE IN THE STUDY.*

Historically occlusion therapy alone has not proved to be very successful with older children and adults. Because we were seeking to complete a statistically significant study on the use of L-dopa to augment occlusion therapy, we needed thirty patients per experimental group. Currently about 3% of children develop amblyopia (120,000/year in the USA) and many never regain normal vision in the amblyopic eye or regain binocular vision. Given the low frequency of amblyopes in the general population, and even smaller number of patients who have anomalous correspondence, the goal of producing a meaningful study in the given time allowance has presented a major challenge to investigators. For researchers interested in continuing with this study in the future, the task of promoting this type of study requires contacting clinicians in the fields of optometry, ophthalmology, pediatrics, learning disabilities, as well as recruiting subjects on university campuses.

It is the hope of the principal investigators that this study be continued by later groups of student investigators such that the results may yield information which can add to the current understanding of a combination L-dopa-occlusion-vision therapy treatment regime. Also, it is a possibility that other ophthalmologists and optometrists may have an interest in a multi-center clinical trial, which could add more useful information on our topic of interest.



#### *DIFFICULTIES IN OBTAINING THE WRITTEN PRESCRIPTION FOR L-DOPA*

In this study we were only able to obtain data for one subject. We had at least two other subjects who were willing to participate in the study but we were unable to obtain a written prescription for the medication. The lead physician who was prescribing the L-dopa discontinued his working relationship with Pacific University. He then became unable to write the L-dopa prescriptions for the patients who had agreed to become subjects in the study. A secondary physician was asked to become involved in the study and write the L-dopa prescriptions but was unable to due to his employment contract with a different university. It would have become necessary to file a new IRB (institutional review board) with the second university for him to become involved. This would have been too economically costly and time consuming. For future investigators it would be recommended to have a backup physician who understands the nature of the research and is comfortable in prescribing L-dopa.

#### *THE PRINCIPAL INVESTIGATORS WERE AWAY FROM THE LOCATIONS THAT WERE PARTICIPATING IN RECRUITING PATIENTS FOR THE STUDY.*

Patient recruitment requires active solicitation of patients, which became difficult for the principal investigators because of the clinic rotation nature of the fourth year of optometry school. At Pacific University the fourth year of optometry school requires rotation of clinic sites every 3 to 4 months. The principal investigators were away at preceptorship sites causing patient recruitment efforts to diminish for two thirds of clinical year.

*USE OF ORALS MEDICATIONS IN AMBLYOPIA THERAPY IS STILL CONSIDERED EXPERIMENTAL AND PROVED TO BE AN OBSTACLE TO PATIENT ENROLLMENT IN THE STUDY.*

Patients generally were reluctant to join the study owing to the novel approach of using L-dopa for the treatment of amblyopia and strabismus. In spite of a significant amount of literature on the use of L-dopa for these patients, it is still considered an off label 'experimental' use of the drug. For future researchers interested in this subject it will be important for the investigators of the study, and any other persons seeking to recruit patients for the clinical trials, to stress anticipated benefits for all those involved. L-dopa may potentiate vision therapy treatment as well as both the outcomes of VT treatment and strabismus surgery. It is the belief of the investigators that improved sensory functioning in amblyopes will give these patients a better stimulus for fusion. This will reduce the number of vision therapy sessions as well as the number of strabismic surgeries required to achieve ocular alignment, and ultimately single binocular vision. This would be of great benefit to these patients as fewer office visits and fewer surgeries would thereby reduce health care costs. We would also like to inform future researchers that potential subjects should know that they will have the opportunity to contribute to our understanding of amblyopia, strabismus and anomalous correspondence. Their participation in this type of research helps pave the way to more efficacious treatments, as well as potentially change the current standard of care. Participants can meaningfully contribute to the advancement of optometric science and the general understanding of these difficult conditions.

*THE VISUAL RISKS OF INTRACTABLE DIPLOPIA AND HORROR FUSIONIS IS ANOTHER DETERRANT TO PARTICIPATING IN THIS STUDY.*

The visual risks subjects potentially encounter are significant deterrents to a patient's willingness to participate in this clinical trial. Currently, there is no guaranteed method of reversing horror fusionis or eliminating intractable diplopia (as its name suggests). Although these conditions are truly rare, patients need to be aware of their possibility and this can intimidate a subject from participation.

*THE EXPENSES REQUIRED FOR THE DRUG REGIMEN AND THE REQUIRED PHYSICAL EXAMS CAN LIMIT PATIENT PARTICIPATION*

The costs of the physical exam required before each subject can begin therapy may be prohibitive for some individuals. As mentioned before, it is required that we record weight, blood pressure, body temperature, heart rate and respiration to monitor any health changes during the testing period. In addition, as it is the patient's responsibility to cover the costs of L-dopa therapy, this can prove to be discouraging from joining the study. To defray the costs of joining the study, we considered asking the drug manufacturer to donate the medication but determined any donations may place the integrity of the study in question. If a financial interest is involved in our study, it may cast doubts on the results upon peer review of the experiment. Additionally, if the patient must purchase the medications, he or she may feel more compelled to comply with the drug regimen. To promote the use of L-dopa to patients, we recommend to future investigators to inform potential subjects that the cost of repeated surgeries to correct regression of strabismus

would far outweigh the costs of the medications. Plus, the use of the oral medication has few side effects relative to the inherent risks of surgery. This approach may appeal to patients as well as parents considering surgical correction of strabismus in their children.

*THE OVERALL LENGTH OF THE STUDY EXCEEDED THE AMOUNT OF TIME AVAILABLE IN THE ACADEMIC CALENDER*

The study is a single-masked, controlled, pseudo-randomized 13-week longitudinal study. The study requires recruiting potential subjects, waiting for the results of the required physical exams before enrolling subjects in the study, and gathering data on all subjects all within the duration of an academic semester. Since patients may be selected for the study at different times, some data may not be available for results analysis. The problem arose in which completion of the study was not possible during two school semesters. It is recommended to future investigators to encourage subjects to schedule a physical examination as soon as they can and to plan for the time lag involved in scheduling and receiving the health report from the primary care physician.

*THE AMOUNT OF TESTS THAT WERE PLANNED FOR EACH PATIENT IN SOME CASES WAS IMPRACTICAL AND LEAD TO PATIENT FATIGUE*

Visual sensory functioning was to be evaluated in terms of visual acuities, contrast sensitivities, level of stereopsis, suppression behavior, and degree of crowding in all patients. Amblyopic patients will also be screened through a battery of several tests to assess the presence and depth of anomalous correspondence. Given the breadth of variables we are testing at each patient visit, a potential problem arose in which there was

not enough time allotted for completion of all the tests. Moreover, the patients who are amblyopic and strabismic often succumb to fatigue during the lengthy period of testing. Thus, it is recommended to future researchers to prepare an abbreviated list of tests that covers the important aspects of the study without excessive redundancy. This is especially pertinent in the cases where duration of testing is too long for the patient's attention span and comfort.

*THE STUDY, AS IS CURRENTLY BEING ADMINISTERED, MAY NOT PROVE BENEFICIAL IN OLDER SUBJECTS OR THOSE WHO'S SENSORY ADAPTATIONS ARE DEEPLY EMBEDDED.*

A possible source of problems in this study is the possibility of failure of L-dopa and occlusion therapy to improve visual sensory functioning if amblyopia and anomalous correspondence are deeply embedded. The experimental nature of L-dopa use in our study will likely require investigators to adjust the dosage levels of the drug. The current dosages and treatment periods used in our study were relatively accepted levels and durations; the dosages and time periods employed have been previously investigated, in particular by Leguire et al <sup>1-9</sup>. We note that other researchers have begun to prescribe L-dopa off-label in treatment of amblyopia. In brief, this drug combination of L-dopa/carbidopa is used in more than a dozen safely established studies and thousands of patients with Parkinson's disease. Not only do we expect changes to be made in L-dopa dosages for different patients, depending on factors such as age, duration of binocular problems, and health status and medications use, but we also expect to the treatment period to be altered as the use of L-dopa is researched further. In our trial the pilot

subject was 67 years old and there was minimal changes noted during L-dopa treatment period. It is difficult to say if the dosage was an important factor. In any case it appears that the longstanding nature of his visual sensory dysfunction proved to be a formidable obstacle in his treatment.

#### *FUTURE STUDIES MAY NEED TO REFINE OUR PROPOSED AC INDEX*

The AC index is calculated for each subject identified with AC, based on the number and magnitude of each of the screening tests. Then, each experimental group was to be assigned an AC index number based on the mean of all index numbers of the group members. These AC indices, which define the level of AC present in the group as a whole, were to be compared to one another for the purposes of assessing effectiveness of the various therapies. The AC index includes with it a certain degree of clinician error that needs to be recognized. It would be beneficial for future researchers to establish an accepted standard error for the proposed AC index as well as the individual component tests. The tests included in the AC index are common optometric clinical means for establishing the presence or absence for Anomalous Correspondence and the validity for these tests are assumed based on their use by clinicians working in this field. Future researchers could help establish which of the tests included in the AC index are the most efficient, reliable, and yield the most accurate results.

In conclusion, we have learned that it is a challenge to develop clinical trials which involve a very minor proportion of the general population, which may incur financial expenses for the patients, which carry threatening risks, and which require testing a large number of variables for an extended amount of time. Moreover, we have developed skills required to formulate comprehensive risk disclosure and informed consent documents as well as understanding the complexity of conditions such as amblyopia, strabismus, and anomalous correspondence. We feel that we have learned a great deal in understanding the procedures for diagnostic testing of these conditions. Finally, we have cultivated a deeper appreciation for the work of previous researchers who have laid the groundwork in innovative treatment approaches in the field of binocular vision, as well as for our project advisors whose deep knowledge base and circumspect minds have enabled us to cultivate our own understanding of treatment of patients with amblyopia and anomalous correspondence.

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**TABLE 1 - Clinical Adverse Experiences Occurring in 1% or Greater of Adult Parkinson's Patients <sup>14</sup>**

Adverse Experience	Carbidopa- Levodopa
	n = 524
	%
Dyskinesia	12.2
Nausea	5.7
Hallucinations	3.2
Confusion	2.3
Dizziness	2.3
Depression	1.3
Urinary tract infection	2.3
Headache	1.9
Dream abnormalities	0.8
Dystonia	0.8
Vomiting	1.9
Upper respiratory infection	1.0
Dyspnea	0.4
'On-Off' phenomena	1.1
Back pain	0.6
Dry Mouth	1.1
Anorexia	1.1
Diarrhea	0.6
Insomnia	1.0
Orthostatic hypotension	1.1
Shoulder pain	0.6
Chest pain	0.8
Muscle cramps	1.0
Paresthesia	1.1
Urinary frequency	1.1
Dyspepsia	1.1
Constipation	1.5

## Appendix A – Forms

**Sinemet Subject Information Sheet**

**(Please print or type)**

Patient Name: \_\_\_\_\_ Date: \_\_\_\_\_

Parent Name(s): \_\_\_\_\_

Address: \_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

Home Phone Number: \_\_\_\_\_  
(with area code)

Work Phone Number: \_\_\_\_\_  
(with area code)

Eye Doctor's Name: \_\_\_\_\_

Patient Birth Date: \_\_\_\_\_

Patient's Gender: \_\_\_\_\_

Patient's Weight (Kg) \_\_\_\_\_

Type of Amblyopia: \_\_\_\_\_

Best Corrected Visual Acuity at Baseline: OD: \_\_\_\_\_ OS: \_\_\_\_\_

Best Corrective Lens, if applicable: OD: \_\_\_\_\_

OS: \_\_\_\_\_

Notes: \_\_\_\_\_

\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

### SYMPTOM CHECKLIST

Patient Name: \_\_\_\_\_ Date \_\_\_\_\_

Visit # Week ☐0, ☐3, ☐7, ☐13 (Check week visit)

Comments: \_\_\_\_\_

Please check Y(Yes) or N(No) for each symptom you experienced

Muscle cramps	<input type="checkbox"/> Y <input type="checkbox"/> N	Eating problems (anorexic)	<input type="checkbox"/> Y <input type="checkbox"/> N
Diarrhea	<input type="checkbox"/> Y <input type="checkbox"/> N	Ringing in ears	<input type="checkbox"/> Y <input type="checkbox"/> N
Tiredness	<input type="checkbox"/> Y <input type="checkbox"/> N	Confusion	<input type="checkbox"/> Y <input type="checkbox"/> N
Nausea	<input type="checkbox"/> Y <input type="checkbox"/> N	Depression	<input type="checkbox"/> Y <input type="checkbox"/> N
Vomiting	<input type="checkbox"/> Y <input type="checkbox"/> N	Urinary problems	<input type="checkbox"/> Y <input type="checkbox"/> N
Dizziness	<input type="checkbox"/> Y <input type="checkbox"/> N	Walking problems	<input type="checkbox"/> Y <input type="checkbox"/> N
Faintness	<input type="checkbox"/> Y <input type="checkbox"/> N	Breathing problems	<input type="checkbox"/> Y <input type="checkbox"/> N
Shaking	<input type="checkbox"/> Y <input type="checkbox"/> N	Chest pain	<input type="checkbox"/> Y <input type="checkbox"/> N
Twitching	<input type="checkbox"/> Y <input type="checkbox"/> N	Back pain	<input type="checkbox"/> Y <input type="checkbox"/> N
Dry Mouth	<input type="checkbox"/> Y <input type="checkbox"/> N	Constipation	<input type="checkbox"/> Y <input type="checkbox"/> N
Headache	<input type="checkbox"/> Y <input type="checkbox"/> N	Eye lid twitch	<input type="checkbox"/> Y <input type="checkbox"/> N
Numbness	<input type="checkbox"/> Y <input type="checkbox"/> N	Muscle spasms	<input type="checkbox"/> Y <input type="checkbox"/> N
Flushing	<input type="checkbox"/> Y <input type="checkbox"/> N	Other (please be specific)	
Circles under eyes	<input type="checkbox"/> Y <input type="checkbox"/> N	_____	
Restless sleep	<input type="checkbox"/> Y <input type="checkbox"/> N	_____	
Nightmares	<input type="checkbox"/> Y <input type="checkbox"/> N	_____	
Mood changes	<input type="checkbox"/> Y <input type="checkbox"/> N		

### SINEMET STUDY CHECKLIST

- ☐ Subject qualifies for study (see exclusion criteria appendix B of Risk Disclosure)
- ☐ Obtained signed consent. Give subject or parent one copy of consent and signature page
- ☐ Physical exam completed by primary care physician
- ☐ Weigh subject, without shoes, in kgs. Weight: \_\_\_\_\_
- ☐ Fill out patient information sheet (needed for randomization).
- ☐ Have Dr. Lenart sign Sinemet prescription
- ☐ Have subject fill-out symptom checklist during visit at week number 0, 3, 7, 13
- ☐ Have subject fill out lazy eye questionnaire during visit at week number 0,3,7,13
- ☐ Give subject or parent 2 cans of Sustacal (free refills if needed)
- ☐ Give subject or parent a box of patches for each week (free refills as needed)
- ☐ Have subject return bottle with remaining Sinemet, if any, at their 7-week appointment.

## AMBLYOPIA QUESTIONNAIRE

PARTICIPANT NAME: \_\_\_\_\_ DATE: \_\_\_\_\_

DATE OF BIRTH: \_\_\_\_\_ SEX: ☐ M ☐ F

1. How many hours each day are you **supposed to wear** your patch? \_\_\_\_\_
2. How many hours each day do you **actually wear** the patch? \_\_\_\_\_

**Questions 3-8 are only applicable if the subject is a child**

3. How difficult is it to put on your child's eye patch? (circle one)  
  
1 2 3 4 5 6 7 8 9 10  
easy          average          extremely difficult
4. How difficult is it to keep your child from removing their eye patch? (circle one)  
  
1 2 3 4 5 6 7 8 9 10  
easy          average          extremely difficult
5. Does your child's behavior change when he or she is wearing the eye patch? If it does, please explain how it changes:  
  
\_\_\_\_\_  
\_\_\_\_\_
6. How have other children reacted when your child is wearing the eye patch?  
  
\_\_\_\_\_  
\_\_\_\_\_
7. Has your child's performance at school changed since patching has begun? If so, how has it changed? \_\_\_\_\_  
\_\_\_\_\_
8. What have you tried in order to keep the eye patch on your child?  
  
\_\_\_\_\_  
\_\_\_\_\_
9. Any other comments you would like to make?  
  
\_\_\_\_\_  
\_\_\_\_\_

**SINEMET STUDY DATA SHEET**

Name: \_\_\_\_\_

Date: \_\_\_\_\_

Week #: (0, 3, 7, 13) \_\_\_\_\_

**BVAT:**

Visual Acuities OD \_\_\_\_\_ OS \_\_\_\_\_ OU \_\_\_\_\_

Single Letter Acuity: OD \_\_\_\_\_ OS \_\_\_\_\_ OU \_\_\_\_\_

Distance Stereopsis: \_\_\_\_\_

Distance Suppression: \_\_\_\_\_

Contrast Sensitivity: (use 2 lines above best acuity, start supra-threshold)

OD \_\_\_\_\_ OS \_\_\_\_\_

**VISAGRAPH:**

Stability of Fixation: OD: \_\_\_\_\_ OS: \_\_\_\_\_ OU: \_\_\_\_\_

Rate: **Good** fixation (0 deviations), **Moderate** fixation stability (1-2 deviations),

**Unstable** fixation (>2 deviations)

**Macular Integrity Tester:**

Central Fixation: ☐ Y ☐ N

Eccentric Fixation: ☐ Y ☐ N If yes prism diopters of eccentricity

\_\_\_\_\_

**Visuoscropy:**

Eccentric Fixation: ☐ Y ☐ N

Objective Estimate of deviation (prism diopters): \_\_\_\_\_ N T S I

**Dissociated Red Lens Test:**

Distance cover test objective neutralization value (prism diopters): \_\_\_\_\_

Subjective response to red lens: Targets overlap: ☐ Y ☐ N

Crossed diplopia ☐

Uncrossed diplopia: ☐

Harmonious AC (objective cover test angle equals subjective)

Unharmonious AC (objective angle differs from subjective by more than 4 prism diopters).

Results: Harmonious AC: ☐

Unharmonious AC: ☐



### Hering Bielchowsky After-Image Test:

Subjective vertical after-image report: \_\_\_\_\_ cm

Direction of angle of anomaly ☐ Crossed ☐ Uncrossed

### Synoptophore:

Superimposition of 1<sup>st</sup> degree targets achieved: ☐ Y ☐ N

Objective angle of 1<sup>st</sup> degree fusion: \_\_\_\_\_ prism diopters

Subjective angle of 1<sup>st</sup> degree fusion: \_\_\_\_\_ prism diopters

(if objective angle equals subjective angle this indicates normal correspondence. If objective and subjective angles differ by more than 4<sup>Δ</sup> this indicates AC)

### Red Green Glasses AC Test

Subject Reports: Luster ☐ Y ☐ N indicates normal correspondence  
Split field ☐ Y ☐ N (one side red, one side green) indicates AC  
Sees Only 1 Color ☐ Y ☐ N (indicates suppression)

### Worth 4-Dot Test

Constant Strabismus present: ☐ Y ☐ N  
Number of Dots seen: ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ Other \_\_\_\_\_  
With neutralization of strabismus using the objective amount of prism:  
How many dots are seen: ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ Other \_\_\_\_\_  
Distance at which subject was tested: \_\_\_\_\_

### Bagolini Striated Lenses

Are 45 & 135 degree lines continuous: ☐ Y ☐ N  
Are there missing segments in either line: ☐ Y ☐ N  
If yes which line: ☐ 135 ☐ 45  
How many lights are seen: ☐ 1 ☐ 2  
If two, where are the lights relative to the intersection of the two lines:  
☐ Above ☐ Below  
Have subject sketch if necessary what is seen by patient

### Random Dot Butterfly Stereo Acuity Test at 40 cm

Highest Level of Stereo acuity seen \_\_\_\_\_ arc seconds